Chapter 22
Synaptic Dysfunction in Schizophrenia

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Abstract Schizophrenia alters basic brain processes of perception, emotion, and judgment to cause hallucinations, delusions, thought disorder, and cognitive deficits. Unlike neurodegeneration diseases that have irreversible neuronal degeneration and death, schizophrenia lacks agreeable pathological hallmarks, which makes it one of the least understood psychiatric disorders. With identification of schizophrenia susceptibility genes, recent studies have begun to shed light on underlying pathological mechanisms. Schizophrenia is believed to result from problems during neural development that lead to improper function of synaptic transmission and plasticity, and in agreement, many of the susceptibility genes encode proteins critical for neural development. Some, however, are also expressed at high levels in adult brain. Here, we will review evidence for altered neurotransmission at glutamatergic, GABAergic, dopaminergic, and cholinergic synapses in schizophrenia and discuss roles of susceptibility genes in neural development as well as in synaptic plasticity and how their malfunction may contribute to pathogenic mechanisms of schizophrenia. We propose that mouse models with precise temporal and spatial control of mutation or overexpression would be useful to delineate schizophrenia pathogenic mechanisms.

Keywords Excitatory synaptic transmission • Inhibitory synaptic transmission • Neuromodulators • Schizophrenia • Schizophrenia susceptibility genes

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22.1 Introduction

Schizophrenia alters basic brain processes of perception, emotion, and judgment to cause hallucinations, delusions, thought disorder, and cognitive deficits. It is a mental disorder that affects 0.5–1% of the population worldwide with devastating consequences for affected individuals and their families and is the seventh most costly illness in the USA. Unlike neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS) that have irreversible neuronal degeneration and death, nerve cells in schizophrenia generally do not degenerate or die. Because of the lack of pathological hallmarks, schizophrenia remains to be one of the least understood psychiatric disorders. With identification of schizophrenia susceptibility genes, recent studies have begun to shed light on underlying pathological mechanisms. All brain functions depend on the function of synapses, connections between neurons. It is now widely believed that schizophrenia results from problems during neural development that lead to improper function of synaptic transmission and plasticity (Eastwood 2004; McCullumsmith et al. 2004; Mirnics et al. 2001; Nikolaus et al. 2009; Stephan et al. 2006). Intriguingly, many of the schizophrenia susceptibility genes encode proteins that have been implicated in synapse formation and/or function. This chapter focuses on the relationship between synaptic transmission and schizophrenia. We will first review evidence for altered neurotransmission at glutamatergic, GABAergic, dopaminergic, and cholinergic synapses in schizophrenia and discuss the roles of susceptibility genes in neural development and synaptic plasticity and how their malfunction may contribute to the pathogenic mechanisms of schizophrenia.

22.2 Altered Synaptic Transmission in Schizophrenia

22.2.1 The Glutamatergic Pathway

The interest in alterations of glutamatergic neurotransmission as potential pathological mechanisms in schizophrenia was raised when phencyclidine (PCP) was found to reduce noncompetitively excitation of neurons by NMDA (Anis et al. 1983). Earlier, PCP had been shown to produce transient psychotic symptoms in healthy individuals including thought disorder, blunted affect, and cognitive impairments that resemble those in schizophrenic patients (Fauman et al. 1976; Luby et al. 1959). Ketamine, a PCP derivative and a dissociative anesthetic drug, was also able to generate in healthy individuals transient schizophrenia-like (positive and negative) symptoms and impair cognitive functions that depend on the prefrontal cortex (PFC) (Adler et al. 1999; Krystal et al. 1994; Lahti et al. 2001; Malhotra et al. 1997). In schizophrenic patients, ketamine exacerbates preexisting symptoms (Lahti et al. 1995; Malhotra et al. 1997). Taken together, these results suggest a role of reduced glutamatergic function in schizophrenic pathology.

In agreement with this hypothesis were findings that glutamate levels, which inversely correlate with the severity of positive symptoms (Faustman et al. 1999), are significantly lower in the cerebrospinal fluid (CSF) and in brain tissues of schizophrenic patients (Kim et al. 1980; Tsai et al. 1995). Glutamate release from synaptosomes prepared from frozen brain samples of schizophrenics was reduced in response to NMDA or kainic acid (Sherman et al. 1991b). In addition, postmortem analysis shows reduced mRNA and enzymatic activity of glutamate carboxypeptidase II (GCP II), the enzyme that degrades the neuropeptide *N*-acetylaspartylglutamate (NAAG), which is a reversible antagonist of NMDA receptors (Hakak et al. 2001; Tsai et al. 1995). It is controversial whether levels of NMDA or AMPA receptors are reduced in schizophrenics. Increased mRNA levels were reported in some studies (Akbarian et al. 1996; Dracheva et al. 2001; Kristiansen et al. 2006) while other studies showed a decrease (Akbarian et al. 1995, 1996; Dracheva et al. 2001; Kristiansen et al. 2006; Mirnics et al. 2000). Morphologically, dendritic length and dendritic spine density are reduced in the cerebral cortex of schizophrenic patients (Garey et al. 1998; Glantz and Lewis 2000) although the density of pyramidal neurons was shown to be increased in the dorsal lateral PFC (DLPFC) in schizophrenics (Selemon and Goldman-Rakic 1999).

Adult rodents, when treated with NMDA antagonists, become hyperactive (Nabeshima et al. 1983; Sturgeon et al. 1979) and are impaired in prepulse inhibition (Bakshi and Geyer 1995; Bakshi et al. 1994), a behavioral deficit thought to model psychotic symptoms. They are also deficient in social interactions, a negative symptom (Sams-Dodd 1995, 1996) and cognition functions such as working memory (Jentsch et al. 1997). Mutant mice which expressed 5% of normal level of NR1 showed behavioral deficits relevant to schizophrenia including hyperactivity, impaired social interaction, and cognitive dysfunction, which can be ameliorated by antipsychotic treatments (Mohn et al. 1999).

Glutamatergic synapses are present on projection cells as well as interneurons. Both could be the target of "glutamatergic hypofunction." Interestingly, in acutely prepared hippocampal slices, GABAergic interneurons were tenfold more sensitive to NMDA receptor inhibitors than were pyramidal neurons (Grunze et al. 1996). Therefore, GABAergic interneurons should be more vulnerable than pyramidal cells to glutamatergic hypofunction. Hypoactivity of GABAergic neurons would result in impaired inhibition of projection cells and thus cognitive deficits. When the essential subunit of NMDA receptor NR1 was selectively eliminated in parvalbumin (PV)-positive interneurons, mutant mice are impaired in spatial working memory, but their spatial open field exploratory activity and their social activity are normal (Korotkova et al. 2010). Interestingly, when NR1 is ablated in about 50% of cortical interneurons during postnatal development, mutant mice exhibit novelty-induced hyperlocomotion and are impaired in mating and nest building (Belforte et al. 2010). These observations suggest that NMDA receptors in different types of interneurons could have distinct functions. Metabotropic glutamate receptors have also been implicated in schizophrenia. Pretreatment with LY354740, a selective agonist for metabotropicglutamate 2/3 (mGlu2/3) receptors, attenuated the disruptive effects of PCP on locomotion, stereotypy, working

memory, and cortical glutamate efflux (Moghaddam and Adams 1998). These results suggest that mGlu2/3 receptor agonists have antipsychotic properties and may provide a new alternative for the treatment of schizophrenia.

22.2.2 The GABAergic Pathway

Dysfunctions of GABA transmission have also been implicated in the processes leading to psychosis (Keverne 1999; Lacroix et al. 2000). Psychotic symptoms in schizophrenia have been found to be correlated with reduced GABAergic inhibition in the medial temporal region (Busatto et al. 1997). GABAergic interneurons, representing about 20–30% of neocortical neurons, are a population that is extremely heterogeneous, varying in morphology, expression of markers, laminar distribution, and electrophysiological properties (Ascoli et al. 2008; Markram et al. 2004). Embedded in the network of principal cells, they innervate different domains of these neurons. For example, basket cells target the somata and proximal dendrites, chandelier cells form axoaxonic synapses on the axon initial segments. Somatostatin (SOM)-positive or Martinotti interneurons innervate distal dendrites and presumably regulate other inputs of principle cells. Thus, it is generally believed that GABAergic interneurons play a critical role in controlling cell excitability, spike timing, synchrony, and oscillatory activity in the mammalian central nervous system (McBain and Kauer 2009). Albeit fewer in number than principal cells, a single GABAergic neuron can innervate multiple principle cells and thus could potentially alter the activity of thousands of downstream neurons.

In situ hybridization studies demonstrated overall reduced levels of the 67-kDa isoform of glutamic acid decarboxylase (GAD67), the primary enzyme of GABA synthesis, in the PFC area 9 of the left hemisphere of schizophrenic brains (Akbarian et al. 1995). Similar results were obtained in a better controlled study of PFC area 9 of the right hemisphere (Volk et al. 2000). The reduction in GAD67 expression may not be due to antipsychotic medications because long-term treatment with haloperidol did not affect GAD67 mRNA expression in the PFC of monkeys (Volk et al. 2000). Moreover, the activity of GAD was significantly reduced in nucleus accumbens, amygdala, hippocampus, and putamen from schizophrenic postmortem brains (Bird et al. 1977). In agreement, GABA release from synaptosomes of schizophrenic brains was decreased (Sherman et al. 1991a, b). These results suggest that decreased GAD67 mRNA expression in the association regions of the neocortex may be a frequent feature of schizophrenia. Moreover, the binding of [^{3}H]nipecotic acid, a ligand for labeling GABA uptake sites, was reported to be reduced in schizophrenic brains (Reynolds et al. 1990; Simpson et al. 1989). In addition, also the mRNA and protein levels of GAT1 (GABA membrane transporter 1), a protein responsible for reuptake of released GABA into nerve terminals, are reduced in the DLPFC of subjects with schizophrenia (Lewis et al. 1999; Volk et al. 2001).

Early studies reported a loss of small neurons in cortical layer II (Benes et al. 1991). However, subsequent studies failed to see a significant reduction of GAD67-

positive neurons (Akbarian et al. 1995; Volk et al. 2000). Similarly, parvalbumin (PV)-positive interneurons were found to be reduced (Beasley and Reynolds 1997) or unchanged (Woo et al. 1997) in DLPFC in schizophrenia. Nevertheless, evidence appeared to be compelling that GABAergic function is reduced in the DLPFC of schizophrenic patients. Maybe as a compensatory mechanism, expression of $GABA_A$ receptor in superficial layers of the cortex of schizophrenic brains was increased (Benes et al. 1992; Hanada et al. 1987).

Intriguingly, GABAergic alternation in schizophrenia appears to be interneuron type specific. GAD67 expression is normal in 70% of GABAergic interneurons in the DLPFC but reduced or undetectable in the remaining 30% GABAergic neurons (Akbarian et al. 1995; Volk et al. 2000). The affected interneurons express PV, whereas those expressing calretinin appeared to be normal (Hashimoto et al. 2003). PV-positive neurons include basket cells that form perisomatic synapses onto pyramidal neurons and chandelier cells that form characteristic linear arrays of terminals (termed cartridges) on the axon initial segments of pyramidal neurons. GAT1 levels appear to be selectively reduced in chandelier axon cartridges in the DLFC of schizophrenic patients (Woo et al. 1998). On the other hand, $GABA_A$ receptors are upregulated on the postsynaptic membranes facing the axon initial segments, probably to compensate deficient GABAergic transmission (Volk et al. 2002).

Reduced GABA signaling from chandelier cells to pyramidal neurons could contribute to the pathophysiology of working memory dysfunction. Networks of PV-positive GABA neurons, formed by both chemical and electrical synapses, give rise to oscillatory activity in the gamma band range, the synchronized firing of a neuronal population at 30–80 Hz (Whittington et al. 2011). Thus, decreased inhibitory GABA transmission in schizophrenic patients might contribute to psychotic symptoms in schizophrenia. Consistent with this hypothesis, disinhibition of the ventral hippocampus by the $GABA_A$ antagonist picrotoxin would result in similar psychosis-related behavioral disturbances such as hyperactivity and decreased PPI (Bast et al. 2001).

22.2.3 The Cholinergic Pathway

The association of cholinergic pathways with schizophrenia was as ancient as the illness was diagnosed. Schizophrenic patients are often heavy smokers (Lohr and Flynn 1992), and acetylcholine-induced convulsion and atropine-induced coma were used to treat schizophrenia (Forrer and Miller 1958). Substantial evidence has accumulated over the years that suggests the involvement of dysfunction, mostly hypofunction, of cholinergic transmission in schizophrenia (Neubauer et al. 1975; Tandon et al. 1989). Acetylcholine modulates transmission of various neurotransmitters including glutamate, GABA, dopamine, and serotonin. Postmortem studies of brains of schizophrenic patients were ambiguous about protein levels and activity of choline acetyltransferase (ChAT), the enzyme crucially involved in the synthesis of acetylcholine, and AChE, the enzyme that degrades acetylcholine. Protein or activity levels were reported as increased, decreased, or unchanged.

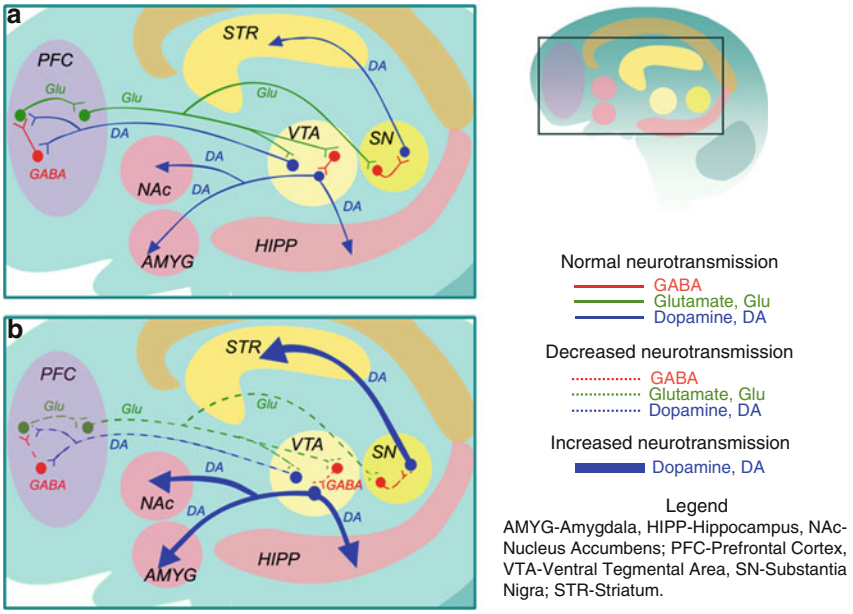

Fig. 22.1 Neurotransmitter pathways in schizophrenia

A more recent study suggested decreased levels of ChAT mRNA and a decreased number of ChAT-positive cells in striatum, particularly in the ventral striatum (Holt et al. 1999, 2005).

Acetylcholine acts by stimulating two types of receptors in the brain: nicotinic and muscarinic receptors. For neuronal nicotinic receptors, there are nine α and three β subunits; the predominant subtypes are the homomeric α7 and heteromeric α4 β2 subtypes (Paterson and Nordberg 2000). There are five types of muscarinic receptors (M1–5), each encoded by an individual gene. A region of chromosome 15, 15q13-14, that contains the α7 AChR subunit gene has been associated with schizophrenia, and SNPs have been described in the promoter region of the α7 subunit gene (Freedman et al. 1997). Studies using postmortem tissue suggest a decreased density of the α7 nicotinic subtype in the brains of schizophrenics (Freedman et al. 1995; Kucinski et al. 2010; Marutle et al. 2001). However, α7 AChR null mutant mice are normal in prepulse inhibition, water maze test, and fear conditioning except for increased anxiety in the open field test (Paylor et al. 1998). Animal studies demonstrate that α7-specific agonists can ameliorate positive and negative symptoms, improve learning and memory (water maze and Y maze), and attentional deficits (auditory gating) (Thomsen et al. 2010; Tregellas et al. 2011). In patients with schizophrenia, α7 agonists appeared to have procognitive effects (Thomsen et al. 2010). These observations suggest that this receptor subtype may be responsible for the inheritance of a pathophysiological aspect of the illness.

As mentioned above, many schizophrenic patients are extremely heavy nicotine users, even in comparison with other psychiatric patients (de Leon et al. 1995;

Hamera et al. 1995). α7 subunit mRNA and protein levels are lower in schizophrenic nonsmokers compared to control nonsmokers and are brought to control levels in schizophrenic smokers (Mexal et al. 2010). Intriguingly, several types of sensory processing deficits, including auditory sensory processing and eye-tracking abnormalities, could be normalized by nicotine, delivered as gum, or by smoking (Adler et al. 1993; Olincy et al. 1998). These observations suggest that schizophrenic patients may smoke to self-medicate endogenous behavioral deficits (Goff et al. 1992).

Initial investigations with quinuclidinyl benzilate (QNB), an antagonist that binds to all five subtypes of muscarinic receptors, were inconsistent on levels of muscarinic receptors in brains of schizophrenic patients. Ligand-binding studies with pirenzepine, an M1-specific antagonist, revealed consistently decreased levels in the DLPFC tissues from subjects with schizophrenia (Scarr et al. 2009). A reduction of pirenzepine binding may be schizophrenia-specific because it was not observed in patients with bipolar disorder or major depression (Zavitsanou et al. 2004). In primates, M1 muscarinic receptors are located postsynaptically in noncholinergic asymmetric and cholinergic symmetric synapses in cortical layers III and V/VI (Mrzljak et al. 1993). They may modulate the cholinergic input from the basal forebrain and intrinsic cortical cholinergic activity (Zhang et al. 2006). M1 mutant mice were normal in hippocampal learning and memory (Miyakawa et al. 2001; Shinoe et al. 2005) but were impaired in behavioral tasks requiring interactions between the hippocampus and cortex (Anagnostaras et al. 2003).

22.2.4 The Dopaminergic Pathway

The original dopamine hypothesis of schizophrenia, proposed over 40 years ago, associates hyperactivity of dopamine transmission with schizophrenia. It was based on effective antipsychotic drugs that appear to act by blocking dopamine D2 receptors and their antipsychotic potency as usually positively correlated with their D2 antagonistic activity (van Rossum 1966). Drugs which inhibit the reuptake of dopamine such as amphetamine can induce schizophrenia-like psychosis in nonpsychotic subjects (Angrist and Gershon 1970; Bell 1973; Gardner and Connell 1972) and exacerbate psychotic symptoms in schizophrenic patients (Laruelle et al. 1999; Lieberman et al. 1987). It was then believed that schizophrenia is associated with hyperactivity of subcortical mesolimbic D2 pathways in the brain. In support of this notion, positron emission tomography studies indicate that schizophrenia is associated with elevated amphetamine-induced synaptic dopamine concentrations (Breier et al. 1997; Laruelle et al. 1996). Striatal dopamine overactivity was observed in patients with "at risk mental states" (ARMS) that might eventually lead to the outbreak of psychosis (Howes et al. 2006).

D2-dependent antipsychotics are effective for positive symptoms but not negative symptoms and cognitive deficits in schizophrenic patients. These functions are mainly controlled by the neocortex where the density of D2 receptors is several

times lower than that of D1 receptors (De Keyser et al. 1988; Hall et al. 1994). D1 receptor–mediated signaling regulates the critical patterns of sustained neuronal firing in the DLPFC during working memory tasks (Sawaguchi 2001; Williams and Goldman-Rakic 1995) and has been shown to be critical for cognitive functions subserved by the DLPFC, such as executive cognition and working memory (Sawaguchi and Goldman-Rakic 1991, 1994). Recent postmortem and imaging studies have suggested that the mesocortical dopaminergic projection to the PFC may be hypoactive (Toda and Abi-Dargham 2007). Dopaminergic axons from mesocortical regions were reduced in the DLPFC of schizophrenic patients (Akil et al. 1999). Probably to compensate for the reduced dopaminergic input, D1 receptor binding in the DLPFC was increased in in vivo imaging studies of drug-free and drug-naive schizophrenia subjects (Abi-Dargham et al. 2002). In some case, the D1 receptor binding was decreased in schizophrenic patients (Okubo et al. 1997). In summary, the D1 upregulation does not actually contribute to the impairment of working memory as D1 receptor antagonist worsen cognitive deficits in schizophrenia (Abi-Dargham and Moore 2003).

22.3 Functions of Schizophrenia Susceptibility Genes in Synapse Formation and Transmission

Many of the schizophrenia susceptibility genes have been implicated in neural development. In addition, recent evidence suggests that they may also regulate neurotransmission and synaptic plasticity. A comprehensive overview about the synaptic function of various schizophrenia susceptibility genes is given below.

22.3.1 D2 DR

Brain imaging studies have found an increase in the density and occupancy of D2 receptors in the striatum of schizophrenic patients (Abi-Dargham et al. 1998; Abi-Dargham et al. 2000; Wong et al. 1986). Also, several studies suggest that at least in a subpopulation of patients the observed increase in D2 receptor binding may be genetically determined (Hirvonen et al. 2004, 2005; Lawford et al. 2005; Zvara et al. 2005). D2 receptors are localized at the postsynaptic membrane of medium spiny neurons in the striatum (Gerfen 1992). In the PFC, where the expression levels of dopamine transporters are low (Sesack et al. 1998), the D2 receptor is localized at dopaminergic terminals to control the reuptake and the release of dopamine (Usiello et al. 2000) and at GABAergic terminals to control the release of GABA (Tseng and O'Donnell 2004). These D2 receptors are thought to fine-tune the firing of pyramidal neurons. Consistent with a major function of D2R as autoreceptors, the ability of dopamine to inhibit the firing of neurons in the midbrain or to inhibit the dopamine

release in striatal projection areas is lost in D2R KO mice (Mercuri et al. 1997; Rouge-Pont et al. 2002). However, no in vivo genetic studies clarified the functions of D2 receptor in GABAergic interneurons. Overexpression of D2 receptor in medium spiny neurons in the striatum causes impairments in cognitive processes in the transgenic mice (Kellendonk et al. 2006). The transgenic mice are also impaired in incentive motivation that relates to negative symptoms. Interestingly, the cognitive, but not motivational, deficits persisted long after D2 receptor expression was switched off, suggesting that transient expression during prenatal development was sufficient to cause cognitive deficits in adulthood.

22.3.2 DISC1

The disrupted in schizophrenia (DISC) gene locus was first identified as a risk factor for major mental illness through study of a large Scottish family in which a balanced translocation between chromosomes 1 and 11 cosegregates with schizophrenia, bipolar disorder, and recurrent major depression (Millar et al. 2000; St Clair et al. 1990). This translocation directly disrupts the DISC1 protein and leads to a C-terminal truncated mutation of DISC1 (Millar et al. 2000). In addition to the translocation, several putative pathogenic mutations have been identified through sequencing DISC1 exons in patients (Song et al. 2008). DISC1 seems to serve as a scaffolding protein interacting with many proteins ranging from transcription factors, phosphodiesterases, and proteins implicated in cytoskeletal and centrosomal organization (Kamiya et al. 2008; Millar et al. 2003, 2005; Miyoshi et al. 2003; Morris et al. 2003; Ozeki et al. 2003). Consistent with this idea, studies in cell culture as well as in *Drosophila* and mice suggest that DISC1 may be involved in neuronal migration, positioning, differentiation, and neurite extension (Duan et al. 2007; Kamiya et al. 2005). DISC1 is expressed at the postsynaptic membrane of asymmetric synapses in human neocortex (Kirkpatrick et al. 2006). Mutant mice were generated to carry a 25-bp deletion in exon 6 of the Disc1 gene, which express a truncated DISC1 protein mimicking the mutant DISC1 found in the Scottish family (Kvajo et al. 2008). These mice exhibit fewer synaptic spines in the dentate gyrus, deficits in short-term plasticity at CA3/CA1 synapses, and impaired working memory (Kvajo et al. 2008). Depletion of DISC1 in newborn neurons in adult mice causes their mispositioning and accelerated formation of dendritic spines and synapses. DISC1-deficient newborn neurons also exhibit enhanced excitability (Duan et al. 2007).

22.3.3 DTNBP1/Dysbindin

Both linkage and association studies have implicated dystrobrevin-binding protein 1 (Dysbindin or DTNBP1) as a promising susceptibility gene for schizophrenia (Kirov et al. 2004; Schwab et al. 2003; Straub et al. 1995, 2002; Tang et al. 2003).

mRNA or protein levels of dysbindin were decreased in prefrontal cortex (PFC) and hippocampus (Talbot et al. 2004; Tang et al. 2009; Weickert et al. 2004, 2008) from schizophrenic patients. Dysbindin is a member of a protein complex, known as biogenesis of lysosome-related organelle complex 1 (BLOC-1). This complex is involved in vesicle trafficking and dendritic branching (Ghiani et al. 2010). In cultured neurons, increase and suppression of dysbindin expression can promote and inhibit glutamate release, respectively (Numakawa et al. 2004). The Sandy mice, which lack dysbindin protein owing to a deletion in the gene Dtnbp1 (encoding dysbindin) (Li et al. 2003), have a decreased rate of vesicle release, a correlated decrease in vesicle pool size, and an increased thickness of the postsynaptic density (Chen et al. 2008). In Sandy mice, deep-layer pyramidal neurons in the PFC showed reduced miniature and evoked EPSCs, and impaired paired-pulse facilitation, suggesting that dysbindin may regulate excitatory transmission in the PFC possibly by a presynaptic mechanism (Jentsch et al. 2009). Decreased levels of dysbindin are associated with reduction in NMDA-evoked currents in PFC pyramidal neurons and in NR1 expression (Karlsgodt et al. 2011). The Sandy mice showed mild deficit in spatial working memory (Jentsch et al. 2009), which appears to correlate with levels of NR1 expression (Karlsgodt et al. 2011).

22.3.4 NRG1 and ErbB4

Several linkage studies in independent populations have identified neuregulin 1 (NRG1) and its receptor ErbB4 as susceptibility genes of schizophrenia (Nicodemus et al. 2006; Norton et al. 2006; Stefansson et al. 2002, 2003; Yang et al. 2003). NRG1 isoforms (types I and IV) and the ErbB4 isoform (JMa, CYT1) are expressed at higher levels in the PFC and hippocampus of schizophrenic patients (Hashimoto et al. 2004; Law et al. 2007; Law et al. 2006; Silberberg et al. 2006). Another group reported a marked increase in NRG1-induced ErbB4 activation in the prefrontal cortex in schizophrenia, while the total level of NRG1 and ErbB4 did not alter (Hahn et al. 2006). NRG1 is a family of EGF domain–containing trophic factors that acts by activating ErbB tyrosine kinases (Mei and Xiong 2008). In vitro studies suggest that NRG1-ErbB4 signaling may regulate neuronal migration and gene expression of NMDA and GABA receptors (Mei and Xiong 2008). However, these notions were challenged by studies of mutant mice (Barros et al. 2009; Brinkmann et al. 2008; Chen et al. 2010a; Gajendran et al. 2009).

ErbB4 in rodents is enriched in GABAergic interneurons (Fazzari et al. 2010; Huang et al. 2000; Lai and Lemke 1991; Vullhorst et al. 2009; Yau et al. 2003). During development, NRG1-ErbB4 appears to play a role in the formation of excitatory synapses on GABAergic interneurons and inhibitory synapses on projection cells (Fazzari et al. 2010; Ting et al. 2011). Both NRG1 and ErbB4 are expressed in adult brain. Acute treatment of hippocampal slices with soluble NRG1 suppresses the induction of long-term potentiation (LTP) (Huang et al. 2000).

Evidence suggests that this effect is mediated by enhanced GABAergic transmission. We have recently demonstrated that NRG1 acts to promote GABA release and thus control the firing of pyramidal neurons and suppresses long-term potentiation (LTP) (Chen et al. 2010b; Huang et al. 2000; Wen et al. 2010; Woo et al. 2007). Ablation of ErbB4 in parvalbumin-positive interneurons causes schizophrenia-relevant phenotypes in mutant mice including hyperactivity, impaired prepulse inhibition, and working memory deficits (Wen et al. 2010).

In addition to inhibitory neurons, ErbB4 is highly expressed in midbrain dopaminergic neurons in rodents, monkeys, and humans (Abe et al. 2009; Steiner et al. 1999; Zheng et al. 2009). NRG1 has been shown to promote dopamine release in the striatum, hippocampus, and medial prefrontal cortex (Kato et al. 2010; Kwon et al. 2008; Yurek et al. 2004). In vitro studies suggest that NRG1 enhances the survival of dopaminergic neurons (Zhang et al. 2004). However, mutant mice where ErbB4 is ablated in the entire brain showed normal structure of the substantial nigra pars compacta and no deficits in motor performance, suggesting that ErbB4 is not required for the development or survival of dopaminergic neurons (Thuret et al. 2004). It will be interesting to generate dopaminergic neuron–specific ErbB4 mutant mice to determine whether NRG1-ErbB4 signaling is important for neurotransmission at dopaminergic synapses.

It is controversial whether NRG1 regulates excitatory synapse formation in pyramidal neurons and glutamatergic transmission. Overexpression of ErbB4 and suppression of its expression by ErbB4 shRNA promoted or inhibited the formation of glutamatergic synapses in pyramidal neurons of neonatal hippocampal slices (Li et al. 2007), suggesting a potential role in excitatory synapse formation. However, when ErbB4 is ablated specifically in CaMKII-positive neurons, it had no effect on basal glutamatergic transmission (Chen et al. 2010b). Acute treatment of soluble NRG1 did not alter paired-pulse facilitation (PPF) (Huang et al. 2000; Iyengar and Mott 2008), suggesting no effects of NRG1 on glutamate release. However, NRG1 mutant mice showed altered PPF and short-term plasticity (Bjarnadottir et al. 2007). Treatment with NRG1 decreased NMDAR-mediated excitatory postsynaptic currents in PFC slices and reduced whole-cell NMDAR currents in acutely isolated PFC pyramidal neurons by elevating intracellular Ca^{2+} and stimulating ERK activity (Gu et al. 2005). In hippocampal slices, however, NRG1 appeared to have little effect on NMDAR- or AMPAR-mediated basic transmission (Chen et al. 2010b). In human postmortem hippocampal tissues, NRG1 could attenuate ligand-induced phosphorylation of NMDA receptors and its association with signaling partners (Hahn et al. 2006).

NRG1 regulates the expression of the α7 nicotinic acetylcholine receptors (nAChRs) (Liu et al. 2001; Sandrock et al. 1997; Usdin and Fischbach 1986; Yang et al. 1998). Consistent with these reports, decreased α7 nAChR mRNA and protein in schizophrenic patients is associated with the genetic variation of NRG1 (Mathew et al. 2007). Recent studies of NRG1 mutant mice indicate that type III NRG1 regulates the axonal targeting of α7 nAChR and is required for the enhancement of hippocampal transmission by nicotine (Hancock et al. 2008; Zhong et al. 2008).

22.3.5 Future Directions

It is clear that synaptic transmission and plasticity are disrupted in schizophrenia. The disruption could be caused by problems that occurred during neural development and/or after brain wiring is complete. Interestingly, Rett syndrome–like neurological deficits of MeCP2 mutant mice can be reversed in adult stage (Guy et al. 2007). It would be important to determine whether this occurs to mutant mice of schizophrenia candidate genes, which would require the reversible transgenic or knockout strategies. Tet-Off system is commonly used to overexpress individual genes which can be reversed by doxycycline (Mayford et al. 1996). Tamoxifen-inducible Cre mice were generated to reactivate the genes by removing the loxP-STOP-loxP cassette (Guy et al. 2007; Hayashi and McMahon 2002). Another important question is to demonstrate the deficit in neural circuitry in schizophrenia. For example, recent studies showed impaired hippocampal-prefrontal synchrony in a genetic mouse model of schizophrenia which has the microdeletion on the human chromosome 22 (Sigurdsson et al. 2010). More recent paper reported that the efficacy of ventral hippocampus input to the nucleus accumbens is reduced in the type III NRG1 heterozygotes mutant mice (Nason et al. 2011). The third question to be addressed is how the dysfunction of different types of GABAergic interneurons contributes to the schizophrenia. Optogenetics, a new emerging technique which enables the activation or inactivation of different types of neurons with spatial and temporal control (Boyden et al. 2005; Gradinaru et al. 2009; Petreanu et al. 2009), is obviously of great advantage to address this question. Recent study demonstrated the critical roles of parvalbumin-positive interneurons in gamma-frequency synchronization in vivo using optogenetics (Sohal et al. 2009). Finally, how can we test the hypothesis that a synaptic defect is responsible for schizophrenia in humans? A direct way would be to study synaptic behavior in the brains of affected individuals, but this can not yet be done in the intact human brain. A possible alternative route involves the production of induced pluripotent stem cells (Takahashi et al. 2007; Yu et al. 2007) from adult cells derived from schizophrenic patients and then inducing these iPS cells to form neurons and synapses. The neuronal culture is also potentially useful in screening the individual antischizophrenia drugs.

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